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- (71) Applicant: **DENTSPLY INTERNATIONAL INC.** *For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*
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(54) Title: **ONE-PART SELF-PRIMING DENTAL ADHESIVE**

(57) Abstract: A dental adhesive composition for bonding dental restoratives to dentin and enamel provides a one-part self-etching, self-priming dental adhesive composition having hydrolysis stable polymerizable acidic adhesive monomers.

ONE-PART SELF-PRIMING DENTAL ADHESIVE

Technical Field

The invention relates to dental adhesive compositions for bonding dental restoratives to dentin and enamel. More specifically the invention provides a one-part self-etching, self-priming dental adhesive composition comprising hydrolysis stable polymerizable acidic adhesive monomers.

Background of the Invention

Presently, self-etching, self-priming dental adhesives are composed of two-part systems due to stability issues of the polymerizable acidic monomers. The stability issues are due to the hydrolysis of acidic and adhesive monomers in water or water/solvent mixtures. Therefore the acidic and adhesive monomers are stored water-free and mixed with the aqueous part just before application.

Frequently, sulfuric acid ester or phosphorous ester groups are employed in acidic polymerizable adhesive monomers. These acidic groups tend to hydrolyze ester moieties within of the monomers. To overcome these disadvantages polymerizable phosphonic esters were proposed (DE 19918974). However, these monomers still comprise hydrolysable (meth)acrylic ester moieties. Recently, hydrolysis stable monomers with phosphonic acid ester groups based on α -(oxo ethyl) acrylate were claimed (DE 19746708). However, the synthesis of these monomers is rather expensive and cost prohibitive for the envisaged applications.

Two-part self-etching, self-priming dental adhesive systems are either applied sequentially or in one step after mixing the two parts. Both procedures have inherent disadvantages due to clinical complications which might occur inbetween sequential steps (saliva or blood contamination) or due to dosing problems when mixing is required prior to the application of the self-etching adhesive.

In order to overcome these clinical problems it would be advantageous to provide the self-etching adhesive as a one-part system eliminating the need of sequential application or premixing.

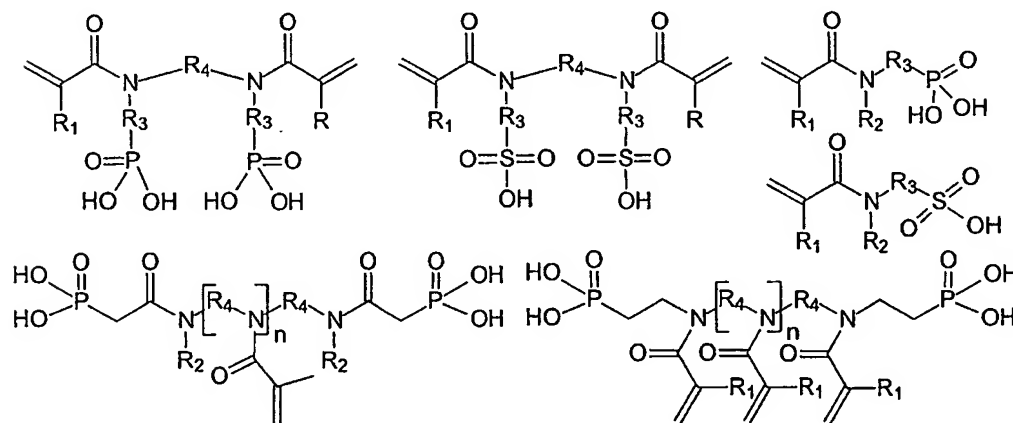
Description of the preferred embodiments

The present invention provides a hydrolysis stable one-part self-etching, self-priming dental adhesive based on (meth)acrylamides and use thereof in polymerizable dental adhesive compositions containing

- i) a polymerizable (meth) acrylamide that comprises at least an organic or inorganic acidic moiety
- ii) a polymerizable monomer
- iii) polymerization initiator, inhibitor and stabilizer.

Preferably the hydrolysis stable one-part self-etching, self-priming dental adhesive comprises at least a carboxylic acid, a phosphoric acid or a sulfuric acid group or most preferably at least a phosphonic or a sulfonic acid moiety.

The polymerizable (meth) acrylamide that comprises at least a phosphonic or sulfonic acid moiety is characterized by the following formulas:



wherein

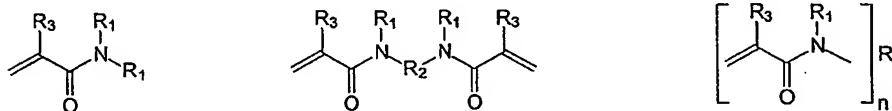
R₁ and R₂ independently are Hydrogen or a substituted or unsubstituted C₁ to C₁₈ alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted C₅ to C₁₈ arylene or heteroarylene, substituted or

unsubstituted C₅ to C₁₈ alkylarylene or alkylheteroarylene, substituted or unsubstituted C₇ to C₃₀ alkylene aryene,

R₃ and R₂ independently are a difunctional substituted or unsubstituted C₁ to C₁₈ alkylene, difunctional substituted or unsubstituted cycloalkylene, difunctional substituted or unsubstituted C₅ to C₁₈ aryene or heteroarylene, difunctional substituted or unsubstituted C₅ to C₁₈ alkylarylene or alkylheteroarylene, difunctional substituted or unsubstituted C₇ to C₃₀ alkylene aryene,

n is an integers.

In addition to the polymerizable (meth) acrylamide that comprises at least a phosphonic or sulfonic acid moiety polymerizable monomers are applied that also have an improved hydrolysis stability, that are characterized by the following formulas:



wherein

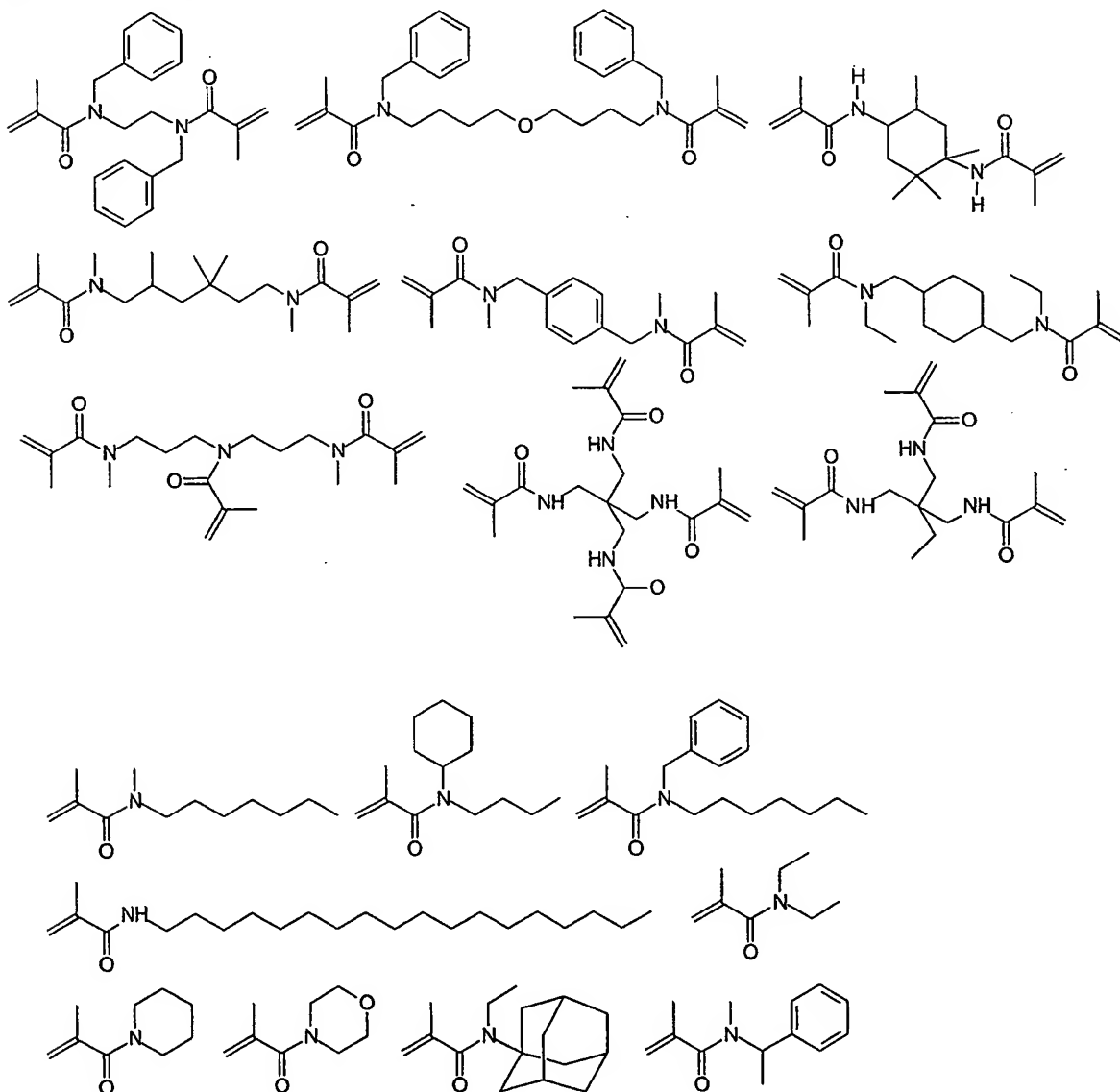
R₁ and R₃ independently are H or a substituted or unsubstituted C₁ to C₁₈ alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted C₅ to C₁₈ aryene or heteroarylene, substituted or unsubstituted C₅ to C₁₈ alkylarylene or alkylheteroarylene, substituted or unsubstituted C₇ to C₃₀ alkylene aryene,

R₂ is a difunctional substituted or unsubstituted C₁ to C₁₈ alkylene, difunctional substituted or unsubstituted cycloalkylene, difunctional substituted or unsubstituted C₅ to C₁₈ aryene or heteroarylene, difunctional substituted or unsubstituted C₅ to C₁₈ alkylarylene or alkylheteroarylene, difunctional substituted or unsubstituted C₇ to C₃₀ alkylene aryene,

R_4 is a mono- or polyfunctional substituted or unsubstituted C_1 to C_{18} alkylene, mono- or polyfunctional substituted or unsubstituted cycloalkylene, mono- or polyfunctional substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, mono- or polyfunctional substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, mono- or polyfunctional substituted or unsubstituted C_7 to C_{30} alkylene arylene,

n is an integers.

The preferably used bis- and mono (meth) acrylamides are characterized by the following formulas:



The claimed compositions comprise at least a bis- or poly (meth) acrylamide, a polymerizable mono acrylamide, an initiator, a stabilizer, water and/or an organic solvent.

The polymerization initiator is a thermal initiator, a redox-initiator or a photo initiator preferably used is champhor quinone.

To stabilize the dental composition as stabilizer are applied radical absorbing monomers such as hydroquinone monomethylether, 2,6-di-tert.-butyl-p-cresol, tetramethyl piperidine N-oxyl radical, galvanoxyl radical.

Example 1

N,N'-Bis (diethyl ethyl phosphonate)-1.2-Bis (2-aminoethoxy) ethane:

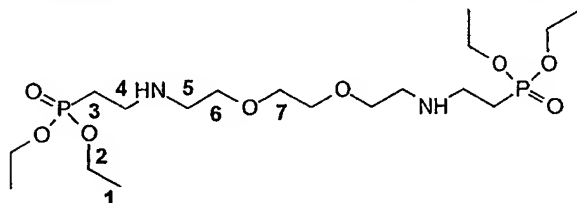
To 11.287 g (0.076 mol) 1.2-Bis (2-aminoethoxy) ethane were added 25.000 g (0.152 mol) Diethyl vinylphosphonate and stirred for 6 hours at 23 °C.

Yield: 36.287 g (100 % d. Th)

(C₁₈H₄₂O₈N₂P₂), 476.49

IR: 3411, 3390 (OH), 2973, 2929, 2885 (CH₂/CH₃), 1390 (CH₂/CH₃), 1078 cm⁻¹ (OH).

¹³C-NMR: 72.1 (6), 70.6 (7), 62.3 (2), 49.9 (5), 34.2 (4), 27.8 (3), 16.4 (1)



N,N'-Bis (diethyl ethyl phosphonate)-N,N'-bismethacrylamido-1.2-Bis (2-aminoethoxy) ethane:

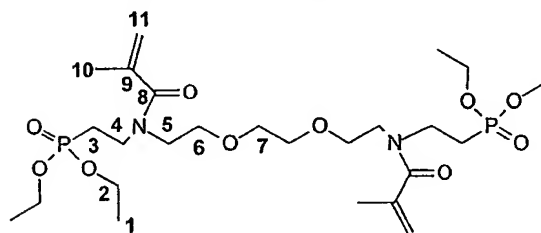
In a 4-necked 1-l-flask equipped with a stirrer, a thermometer and two 50 ml dropping funnels 30.000 g (0.063 mol) of N,N'-Bis (diethyl ethyl phosphonate)-1.2-Bis (2-aminoethoxy) ethane were dissolved in 300 ml of methylene chloride. After cooling to 0-5 °C 13.164 g (0.126 mol) of methacryloyl chloride dissolved in 30 ml of methylene chloride and 5.036 g (0.126 mol) of NaOH dissolved in 15.106 ml of water were added simultaneously under stirring during 1.5 hours so that the temperature remains at 0-5 °C. Thereafter the mixture were stirred at room temperature for additional two hours. Than the reaction mixture were hydrolyzed with 60

ml of ice-water. The organic phase were separated and the aqueous solution were extracted twice with methylene chloride. The collected organic liquids were washed with 50 ml of 1 n HCl, 50 ml of 1 n NaHCO₃ and sometimes with 50 ml of deionised water until the water shows a pH-value of approximately 7. Than the organic solution was dried over NaSO₄. Thereafter the NaSO₄ was filtered off and to the solution 0.039 g of 2,6-di-tert.-butyl-p-cresol were added. The methylene chloride was removed at 40 °C in vacuum and the bismethacrylamide was dried.

Yield: 32 g (83 % of th.)

(C₂₆H₅₀O₁₀N₂P₂), 612.64

¹³C-NMR: 167.7 (8), 140.2 (9), 121.7 (11), 70.6 (6), 69.4 (7), 62.3 (2), 48.2 (5), 32.5 (4), 25.1 (3), 19.3 (10), 16.4 (1)



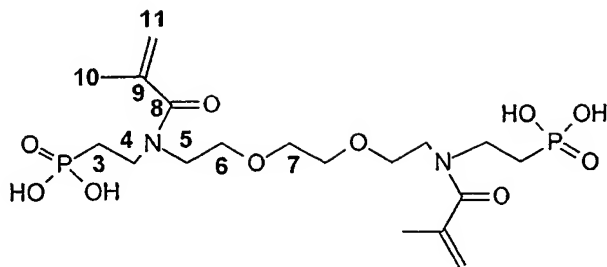
N,N'-Bis (ethyl phosphonic acid)-N,N'-bismethacrylamido-1.2-bis (2-aminoethoxy) ethane:

In a 4-necked 1-l-flask equipped with a stirrer, a thermometer, reflux cooler with CaCl₂-drying tube and 50 ml dropping funnels 30.000 g (0.049 mol) of N,N'-Bis (diethyl ethyl phosphonate)-N,N'-bismethacrylamido-1.2-Bis (2-aminoethoxy) ethane were dissolved in 100 ml of methylene chloride. Then 16.494 g (0.108 mol) Trimethyl bromsilane were added dropwise over an period of 20 minutes under stirring. Thereafter the reaction mixture was stirred for additional 2 hours. By adding of 100 methanol the phosphonic acid silylesters were hydrolyzed. Prior to remove the solvents BHT was added and the product was dried at 40 °C in vacuum.

Yield: 19.11 g (78.0 % d. Th)

(C₁₈H₃₄O₁₀N₂P₂), 500.42

¹³C-NMR: 164.7 (8), 140.2 (9), 121.7 (11), 70.6 (7), 69.4 (6), 48.2 (5), 31.9 (4), 29.5 (3), 19.3 (10)



Example 2

(Bis(3-methacryloylamidopropyl) diethylphosphonic acid ethylester:

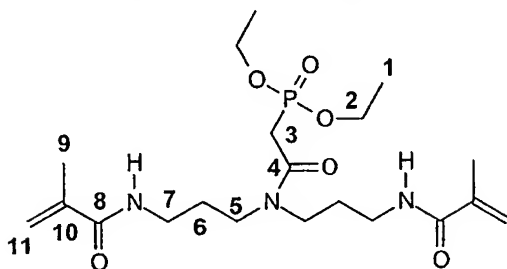
58.073 g (0.443 mol) Bis(3-aminopropyl)amine, 184.454 g (0.894 mol) Dicyclohexyl carbodiimide and 8.651 g (0.071 mol) dimethylamino pyridine were dissolved in a mixture of 250 ml CH_2Cl_2 and 100 ml Acetone. To the cooled mixture ($< 5^\circ\text{C}$) were added 76.200 g (0.885 mol) Methacrylic acid dissolved in 100 ml CH_2Cl_2 so that temperature do not pass 10°C . Then the mixture were stirred for 15 minutes at 0°C and for 20 hours at room temperature. Thereafter the reaction mixture was cooled again and 92.227 g (0.447 mol) Dicyclohexyl carbodiimide dissolved in a mixture of 50 ml CH_2Cl_2 and 50 ml Acetone were added. To this mixture was dropped a solution of 86.804 g (0.443mol) Diethylphosphonic acid ethylester dissolved in 100 ml Acetone so that temperature do not pass 10°C . Then the mixture were stirred for 15 minutes at 0°C and for 20 hours at room temperature. After this time the precipitated solid was filtered off. To the filtrate were added 0.101 g BHT and the solvent was removed by vacuum distillation. The viscose residue was dissolved in 300 ml CH_2Cl_2 and cooled to 0°C . The precipitating solid was removed and the filtrate was washed twice with 150 ml 1n HCl, 150 ml 1n NaHCO_3 solution and with 150 ml water. Furthermore, the solution was dried over NaSO_4 and the solvent was removed. Than the solid was dissolved in Acetone again and dicyclohexyl urea was filtered of. Prior to remove the solvent, 0.197 g BHT was added, the product was dried in vacuum.

Yield: 155.7 g (79.0 % of th.)

($\text{C}_{20}\text{H}_{36}\text{N}_3\text{O}_6\text{P}$), 445.50

IR: 3010/2933/2856 (CH_2/CH_3), 1695 (CO), 1653/1627 ($\text{C}=\text{C}$), 1452 (CH_2/CH_3), 1251 cm^{-1}

^{13}C -NMR: 169.1 (4), 166.5 (8), 140.2 (10), 121.7 (11), 61.6 (2), 44.6 (5), 43.0 (7), 27.9 (6), 27.7 (3), 19.0 (9), 16.4 (1)



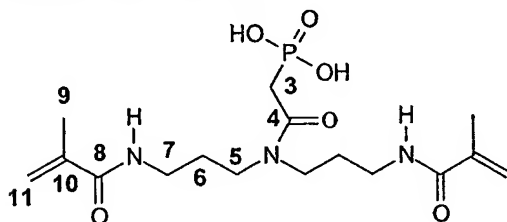
(Bis(3-methacryloylamidopropyl) diethylphosphonic acid:

In a 4-necked 1-l-flask equipped with a stirrer, a thermometer, reflux cooler with CaCl_2 -drying tube and 100 ml dropping funnel 155.700 g (0.350 mol) of (Bis(3-methacryloylamidopropyl) diethylphosphonic acid ethylester were dissolved in 100 ml of methylene chloride. Then 117.77 g (0.769 mol) Trimethyl bromsilane were added dropwise over an period of 60 minutes under stirring. Thereafter the reaction mixture was stirred for additional 2 hours. By adding of 250 methanol the phosphonic acid sylesters were hydrolyzed. Prior to remove the solvents 0.157 g BHT were added and the product was dried at 40 °C in vacuum.

Yield: 115.0 g (84.5 % d. Th)

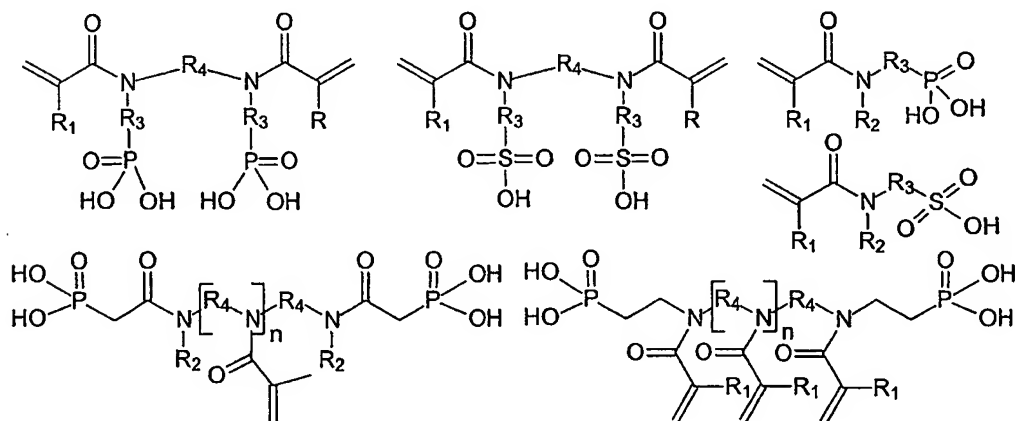
($\text{C}_{16}\text{H}_{28}\text{O}_6\text{N}_3\text{P}$), 389.39

^{13}C -NMR: 169.1 (4), 166.5 (8), 140.2 (10), 121.7 (11), 44.6 (5), 43.0 (7), 27.9 (6), 32.1 (3), 19.0 (9)



We claim

1. Hydrolysis stable one-part self-etching, self-priming dental adhesive comprising
 - (i) an acidic polymerizable (meth) acrylamide that comprises at least an organic or inorganic acidic moiety
 - (ii) a polymerizable monomer
 - (iii) polymerization initiator, inhibitor and stabilizer.
2. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said acidic polymerizable (meth) acrylamide comprises an organic or inorganic acidic moiety, preferably a carboxylic acid, phosphoric acid, sulfuric acid group and most preferably a phosphonic or sulfonic acid moiety.
3. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said acidic polymerizable (meth) acrylamide is selected from the group consisting of:



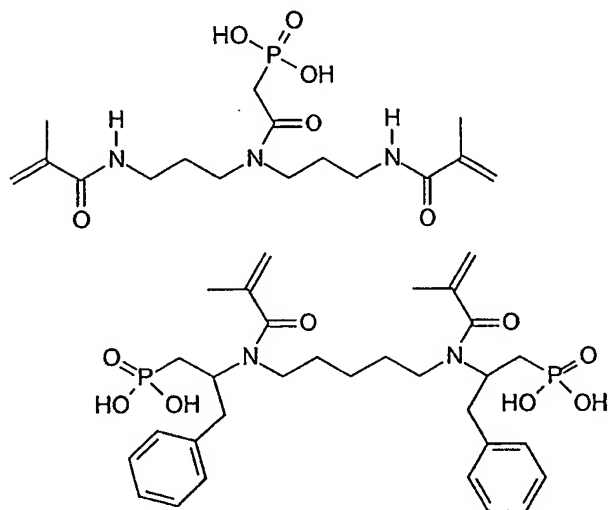
wherein

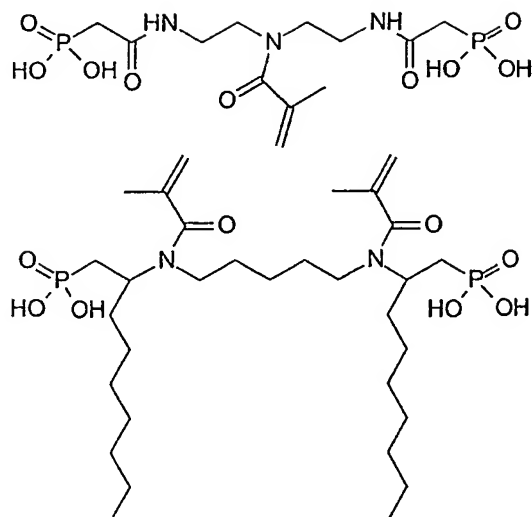
R_1 and R_2 independently are Hydrogen or a substituted or unsubstituted C_1 to C_{18} alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, substituted or unsubstituted C_7 to C_{30} alkylene arylene,

R_3 and R_2 independently are a difunctional substituted or unsubstituted C_1 to C_{18} alkylene, difunctional substituted or unsubstituted cycloalkylene, difunctional substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, difunctional substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, difunctional substituted or unsubstituted C_7 to C_{30} alkylene arylene,

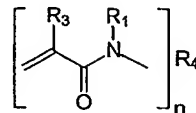
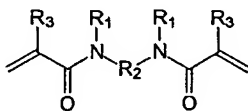
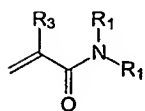
n is an integers.

4. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claims 1 to 3, wherein said acidic polymerizable (meth) acrylamide is selected from the group consisting of:





5. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein polymerizable monomer is selected from the group consisting of:



wherein

R_1 and R_3 independently are H or a substituted or unsubstituted C_1 to C_{18} alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, substituted or unsubstituted C_7 to C_{30} alkylene arylene,

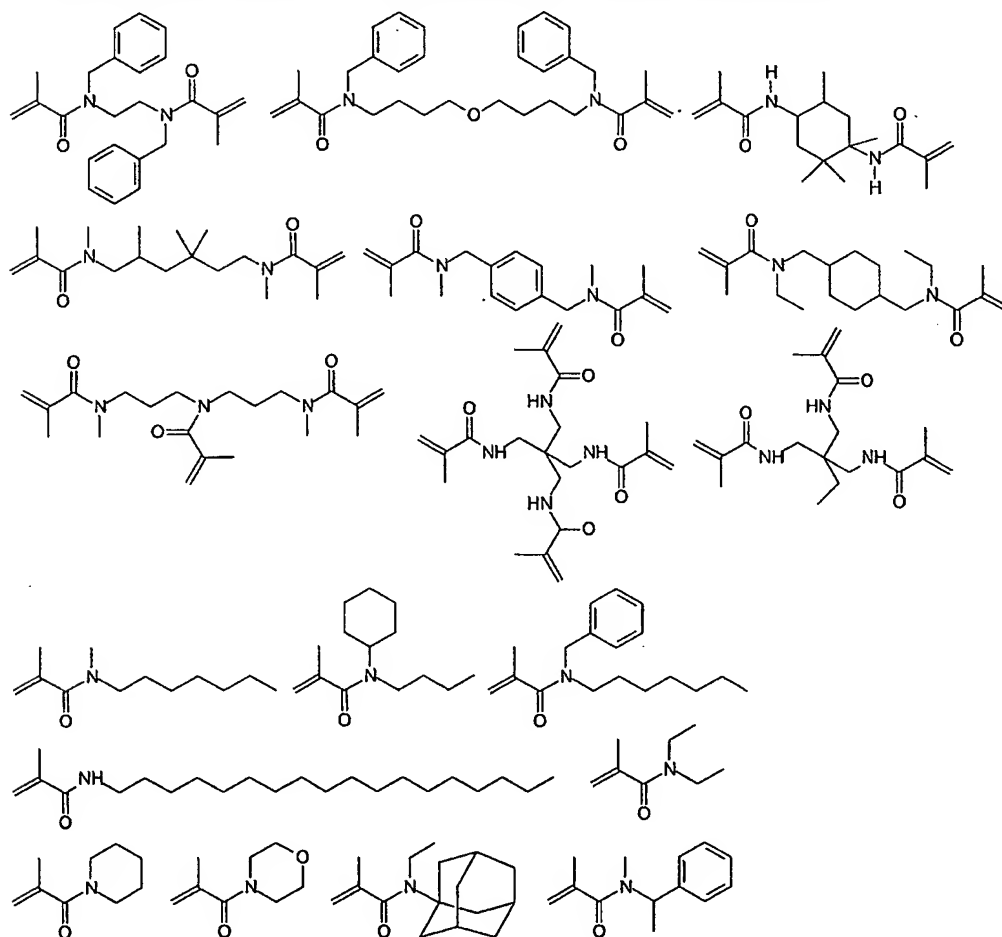
R_2 is a difunctional substituted or unsubstituted C_1 to C_{18} alkylene, difunctional substituted or unsubstituted cycloalkylene, difunctional substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, difunctional substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, difunctional substituted or unsubstituted C_7 to C_{30} alkylene arylene,

R_4 is a mono- or polyfunctional substituted or unsubstituted C_1 to C_{18} alkylene, mono- or polyfunctional substituted or unsubstituted cycloalkylene,

mono- or polyfunctional substituted or unsubstituted C_5 to C_{18} arylene or heteroarylene, mono- or polyfunctional substituted or unsubstituted C_5 to C_{18} alkylarylene or alkylheteroarylene, mono- or polyfunctional substituted or unsubstituted C_7 to C_{30} alkylene arylene,

n is an integers.

6. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said polymerizable monomer is a mono-, bis- or poly(meth) acrylamide that is selected from the group consisting of:



7. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, comprised of at least an acidic polymerizable (meth) acrylamide, a polymerizable monomer, an initiator, a stabilizer, pigments, an organic and/or inorganic filler.

8. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, comprising at least an acidic polymerizable (meth) acrylamide, a polymerizable monomer, an initiator, a stabilizer, water or organic solvent.
9. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, comprising of at least an acidic polymerizable (meth) acrylamide, a polymerizable monomer, an initiator, a stabilizer, pigments, an organic and/or inorganic filler, water or/and an organic solvent.
10. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said polymerizable monomers are applied in a content of 0 to 90 wt-%.
11. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said polymerization initiator is a thermal initiator, a redox-initiator or a photo initiator.
12. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said photo initiator preferably is champhor quinone.
13. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said filler is an inorganic filler and/or an organic filler; preferably the filler is a nanofiller.
14. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said stabilizer is a radical absorbing monomer such as hydroquinone monomethylether, 2,6-di-tert.-butyl-p-cresol.
15. Hydrolysis stable one-part self-etching, self-priming dental adhesive of claim 1, wherein said organic solvent preferably is acetone, ethanol or tert.-butanol.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 02/25005

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K6/00 A61K6/083

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 174 935 B1 (AKAHANE SHOJI ET AL) 16 January 2001 (2001-01-16) example 20 claims	1-15
X	EP 1 057 468 A (KURARAY CO) 6 December 2000 (2000-12-06) paragraphs '0016!', '0029!', '0035! claims	1-15
X	US 5 925 690 A (OHNO HIDEKI ET AL) 20 July 1999 (1999-07-20) column 19, line 19 -column 20, line 9 example 59 claims	1-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * & * document member of the same patent family

Date of the actual completion of the international search

4 November 2002

Date of mailing of the international search report

13/11/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 02/25005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 811 368 A (TOKUYAMA CORP) 10 December 1997 (1997-12-10) page 3, line 49 - line 53 claims -----	1-15
P,X	US 2002/016384 A1 (MOSZNER NORBERT ET AL) 7 February 2002 (2002-02-07) claims -----	1-15
P,X	WO 02 02057 A (ERDMANN CHRISTOPH ;ERNST MUEHLBAUER GMBH & CO KG (DE); MUEHLBAUER) 10 January 2002 (2002-01-10) claims -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati

Application No

PCT/US 02/25005

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6174935	B1	16-01-2001	JP 11180814 A DE 19859989 A1 GB 2332911 A ,B	06-07-1999 01-07-1999 07-07-1999
EP 1057468	A	06-12-2000	AU 3644700 A CA 2309004 A1 CN 1277834 A EP 1057468 A1 JP 2001049199 A	07-12-2000 30-11-2000 27-12-2000 06-12-2000 20-02-2001
US 5925690	A	20-07-1999	NONE	
EP 0811368	A	10-12-1997	EP 0811368 A1 US 5866631 A WO 9723191 A1 JP 9227325 A	10-12-1997 02-02-1999 03-07-1997 02-09-1997
US 2002016384	A1	07-02-2002	DE 10018968 C1 CA 2344134 A1 EP 1148060 A1 JP 2002012598 A	10-01-2002 17-10-2001 24-10-2001 15-01-2002
WO 0202057	A	10-01-2002	EP 1169996 A1 WO 0202057 A1	09-01-2002 10-01-2002